ORIGINAL ARTICLE

Preoperative Changes in Body Weight in Patients with an Insulinoma

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ABSTRACT

Background An insulinoma is an insulin-secreting neoplasm of the pancreas. In the period from first symptoms to treatment, patients with an insulinoma can experience hypoglycemic symptoms repeatedly. Some patients gain weight when they relieve insulinoma-induced hypoglycemic symptoms by ingesting excess food. In this study, we focus on the changes in body weight in patients with an insulinoma and the relationships of those changes to other clinicopathological factors and clinical data. **Methods** Patients with insulinoma who underwent curative surgical treatment at Kagoshima University Hospital, Kagoshima, Japan, between 1995 and 2016 were enrolled in this study and their clinical status was evaluated retrospectively. **Results** Among the 19 patients enrolled, 8 (42%) gained weight and 1 (5%) lost weight. The median monthly net change in body weight was 0.58% (range, -3.9 to 7.0) between onset of the first symptom and until surgery. When we evaluated the relationships among tumor size, serum glucose, serum insulin concentrations and body weight change, a significant correlation was observed among tumor size, serum insulin concentrations and body weight change. Serum glucose concentrations had no significant correlation with other factors. **Conclusion** Based on the results of this study, changes in preoperative body weight was one of the important parameters linked to severe clinical manifestations of insulinoma.

INTRODUCTION

An insulinoma is an insulin-secreting neoplasm of the pancreas. A common symptom of insulinoma is a hypoglycemic state which presents clinically as Whipple's triad, although symptoms are reported as varied with an insulinoma [1]. The estimated incidence of insulinoma is 1–4 cases per million person-years making it a rare disease [2]. Consequently, the diagnosis of insulinoma is difficult and often delayed [1, 3]. In the period from first symptoms until treatment, insulinoma patients can experience repeated hypoglycemic events. Some patients gain weight when they relieve insulinoma-induced hypoglycemic symptoms by ingesting excess food [1]. In this study, we focus on the changes in body weight in patients with an insulinoma and the relationships of those changes to other clinicopathological factors and clinical data.

PATIENTS AND METHODS

Nineteen patients with insulinoma who underwent curative surgical treatment at Kagoshima University Hospital, Kagoshima, Japan, between 1995 and 2016 were enrolled in this study. Clinical information, including age, gender, symptoms, and various data from examinations were obtained from medical records retrospectively. The onset of insulinoma was defined at the time when first syndrome related with insulinoma was appeared. The time was decided by the interview for the patients and information from their previous doctors. Body weight change from the first syndrome to the operation was taken by interviews for each patient. All interviews were done before the operation independently from this study.

Patients had undergone several blood chemistry tests before treatment, so we collected as much data as possible. Excluding data during various load tests, we extracted the minimum serum glucose and maximum serum insulin concentrations among collected data and adopted them as data representative of each patient. All patients provided written informed consent before data acquisition. This study was approved by the Institutional Review Board of Kagoshima University Hospital.

Statistical analysis was performed using JMP Pro, version 12.1.0 for Mac OS (SAS Institute Japan Ltd., Tokyo, Japan). *P* values of less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The clinicopathological features of our cohort are shown in **Table 1**. This study included 19 patients (14 women [74%] and five men), average age 52.5 years, average weight just before operation 70.0 kg. All patients had been diagnosed with insulinoma before surgery and

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Table 1. Clinicopathological features of insulinoma patients.

age (mean, range)	52.5 (22, 79)
gender (male/female)	5 / 14
benign / malignant	18 / 1
solitary / multiple	18 / 1
MEN1	2
tumor size (mm, mean, range)	15.6 (9, 40)
time between first syndrome to operation (months, mean, range)	31.2 (2, 216)
body weight at the time of first symptom (kg, mean, range)	57.2 (43, 91)
body weight change from first symptom to operation (kg, mean, range)	3.8 (-10, 16)
monthly body weight change from first symptom to operation (%, mean, range)	0.58 (-3.9 to 7.0)
minimum serum glucose (mg/dl, mean, range)	39.3 (15, 84)
frequency of examination for serum glucose (mean, range)	7.7 (1, 33)
maximum serum insulin (μIU/ml, mean, range)	35.1 (3.8, 141.3)
frequency of examination for serum insulin (mean, range)	3.4 (1, 7)
observation period (month, mean, range)	59.8 (2, 180)
Recurrence	0
Dead by insulinoma	1 (5%)

were confirmed pathologically. One patient (5%) had multiple lesions, and the one other patient (5%) had a malignant insulinoma. Two patients (11%) were found to also have multiple endocrine neoplasia type 1 (MEN1). Between the first symptom and surgery, the median time that elapsed was 31.2 months (range, 2 to 216). Eighteen of 19 patients had obvious symptoms related hypoglycemic state, but 1 patient had only epigastric pain. For him, we consider epigastric pain was the symptom by insulinoma.

Of the 19 patients, 8 patients (42%) gained weight and 1 patient (5%) lost weight. The median monthly net change in body weight was 0.58 (range, -3.9 to 7.0) between the first symptom and surgery. Overall, among patients the average minimum serum glucose was 39.3 mg/dL and the average maximum serum insulin was 35.1 μIU/mL. After a mean follow-up period of 59.8 months, no patients, other than the patient with a malignancy who had a 40 mm tumor, was dead by insulinoma. This patient had liver metastasis before operation and died 39 months after operation. This patient had a minimum serum glucose of 33 mg/dL and his maximum serum insulin was 141.3 μIU/mL. Within the 3 months prior to surgery, this patient had an 18% increase in his body weight.

Relationships among Various Clinical Data

First, the relationships between tumor size, serum blood glucose, and serum insulin concentrations were examined. The size of each tumor was based on pathological findings, and the one multiple tumor case was excluded. Among the many preoperative serum values documented for glucose and insulin, we elected to evaluate minimum serum glucose values and maximum serum insulin values. The relationships between these values are shown in **Figure 1**. A significant correlation was evident only between tumor size and serum insulin concentrations. The analysis of monthly changes in body weight from the time between the first symptoms until surgery showed significant correlations with tumor size and serum insulin concentrations, but not significant correlation with serum glucose concentrations **(Figure 2)**.

DISCUSSION

In this study, we examined the relationships between various preoperative clinical laboratory data of patients with insulinoma who had a varied disease presentation. This disease characteristic can make the diagnosis of insulinoma difficult. These patients typically report a variety of hypoglycemic symptoms that differ in frequency from patient to patient. Frequent symptoms often induce patients with insulinoma to eat many times in a day in order to mitigate their symptoms which can result in a net increase in their body weight. In fact, a gain in body weight is one of the most common signs of insulinoma and occurs in 39–42% of patients [1, 4]. In our analysis, eight patients (42%) gained weight and one patient (5%) lost weight, a finding that is consistent with previous reports [1, 4]. We hypothesized that changes in body weight occurring from symptom onset until the time of surgery reflect the severity of the disease process in patients with insulinoma. The duration of this period differed among patients, so we used monthly changes in body weight during our analysis. When we evaluated the relationships between tumor size and serum glucose, as well as between tumor size and serum insulin, only serum insulin concentrations were significantly correlated **(Figure 1)**. And we determined that monthly changes in body weight were significantly correlated with tumor size and serum insulin concentration **(Figure 2)**. Based on these results, we propose that changes in body weight reflect the clinical characteristics of insulinoma as well as the severity of clinical findings for this disease to some extent. To the best of our knowledge, correlations between changes in body weight and other clinical factors in patients with insulinoma have not been reported previously.

In our study cohort, the one patient who lost weight preoperatively was treated with diazoxide after diagnosis and experienced nausea and loss of appetite, adverse effects that contributed to the decrease in body weight at that time. Diazoxide is a nondiuretic benzothiadiazine derivative used for relieving hypoglycemic symptoms in

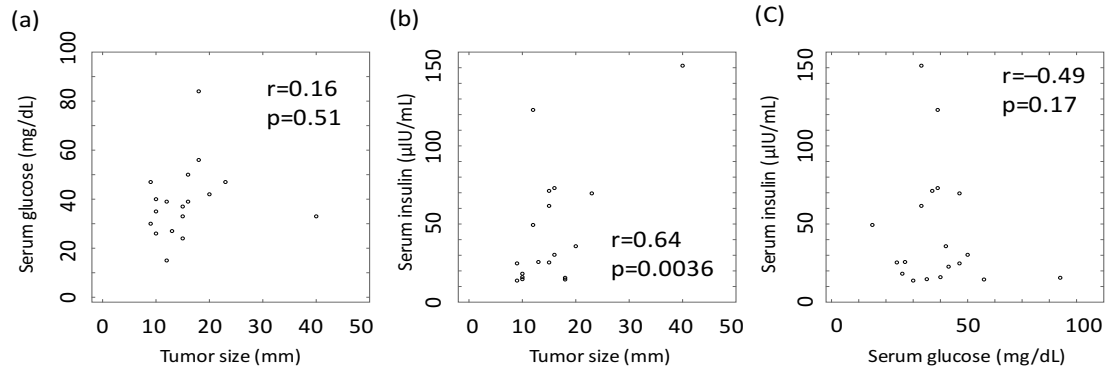

Figure 1. The relationship between **(a).** tumor size and serum glucose and **(b).** tumor size and serum insulin and **(c).** serum insulin and serum glucose. Each correlation coefficient and p-value is shown.

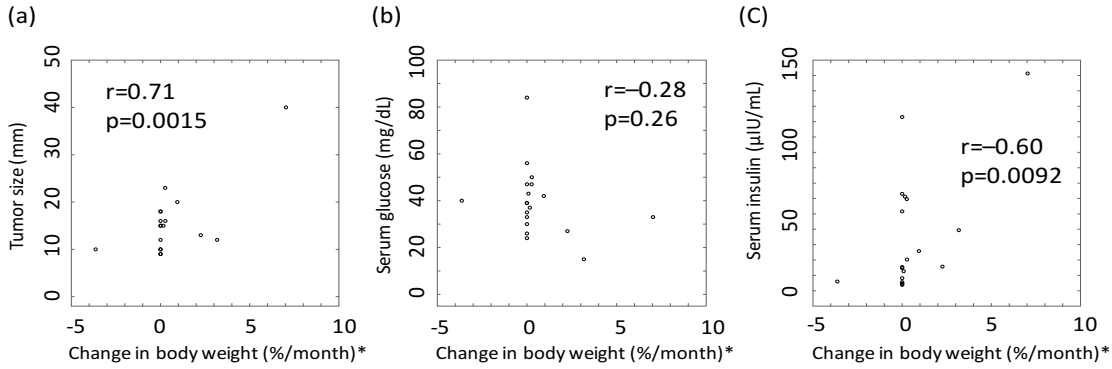

Figure 2. The relationships between **(a).** tumor size and change in body weight **(b).** serum glucose and change in body weight, and **(c).** serum insulin values and change in body weight. *Change in body weight is from first symptoms until surgery. Each correlation coefficient and p-value is shown.

patients with insulinoma [5, 6]. In total, adverse effects were reported for 4 out of 4 patients treated with diazoxide in our cohort and overall, diazoxide use was intermittent. Three of these patients gained weight, and as previously described, one patient lost weight preoperatively indicating our data were not affected by diazoxide usage, but rather the outcomes reflect the natural course of insulinoma in these patients.

The criteria for insulinoma are plasma glucose <55 mg/dL, serum insulin of at least 3.0 μU/mL, and C-peptide of at least 0.6 ng/mL [7, 8]. In our cohort, the criteria were met by 17 out of 19 patients (89%) for glucose and all 19 patients (100%) met the insulin criteria. Laboratory data were collected for patients across several hospitals at multiple time points, yielding several values for each patient; however, we elected to evaluate the minimum glucose concentrations and maximum insulin concentrations of patients. C-peptide was not evaluated in this study because it was not consistently examined or documented for our cohort. Various load tests, such as the leucine loading test, tolbutamide test, and glucagon test [9, 10] were also not routinely performed; hence, we could not properly evaluate those results in this study. Fifteen patients (79%) underwent arterial stimulation venous sampling [11, 12] for diagnosis of localization of insulinoma preoperatively.

Limitations of this study include the small number of patients given the rarity of this disease and our cohort did not include patients with insulinoma who were not treated surgically. To further elucidate the clinical features of insulinoma, it will be necessary to evaluate a larger number of patients independent of treatment procedures.

CONCLUSION

Preoperative changes in body weight were significantly correlated with tumor size and serum concentrations of insulin, but not with serum concentrations of glucose. Preoperative changes in body weight are one of important parameters indicative of the severity of insulinoma.

Conflict of Interest

All authors had no conflicts of interest.

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